

# Working Around the Impending Antibiotic Crisis

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## **Abstract**

Antibiotics are recent advancements of medical technology, but their misuse and overuse have given rise to a variety of problems related to bacteria evolving resistance to these miracle drugs. Unlike other medicinal drugs, antibiotics usage needs to be properly cared via the ideas of antibiotic stewardship for preserving their effectiveness for all members of the public, otherwise currently available drugs will lose their ability to combat illnesses. The supply shortage of viable antibiotic agents is also heightened by the expensive nature of conducting research and development necessary to identify new sources, and the economic unwillingness of most pharmaceutical companies to invest towards working on finding these new antimicrobials. Continuing down this path would lead to a post-antibiotic world that would not be favorable to the modern lifestyle of humankind. However, many opportunities still exist for working to preserve the efficacy of current antibiotics while supporting investments to develop new antibiotics, and this thesis highlights a number of suggestions for how people can work together towards ensuring that antibiotic agents are properly handled and cared for going into the future as well as some ideas that scientists can investigate for pursuing additional means of attacking bacterial infections.

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# **Working Around the Impending Antibiotic Crisis**

## **Introduction to Modern Antibiotics**

Antibiotics as humanity presently understands them were developed in the last 100 years and are considered to be a medicinal “miracle drug” or “wonder drug” due to their capabilities for fighting against historically dangerous infectious diseases. Even though ancient humankind had been aware of the capabilities that certain herbs had in treating against diseases and passed this knowledge down through traditional medicine techniques, it was only relatively recently that Paul Ehrlich and Alexander Fleming were able to devise and implement the scientific methods that comprise modern methods for isolating antibiotic agents (Aminov 2010). Ehrlich utilized a systematic approach towards identifying a drug that would only target syphilis bacteria and leave normal, healthy cells alone and unaffected, thus paving the way for pharmaceutical companies to find “magic bullet” agents for other bacterial diseases as well. Fleming, credited with discovering penicillin from examining the inhibition zones of *Penicillium* mold on agar plates, dedicated many years of research to develop an analysis method for purifying and stabilizing the active parts of antibiotic agents in order to include them in pharmaceutical drugs for easier distribution across the general public. Through a combination of their groundbreaking work, the pharmaceutical industry began to discover and manufacture a variety of antibiotic drugs for treating some common infections found among humans, and helped spread the prevalence of antibiotics around the world as an easy solution for the general public.

With the advent of common antibiotic drugs being produced came a whole set of improvements to the quality of other medical treatments. Some fields of medicine, such as surgery, picked up antibiotic usage to help patients successfully recover after the procedure without developing undesirable diseases, while a number of other important fields, including

cancer chemotherapy or organ transplants and those working with patients having suppressed immune systems, came to require having available antibiotic prescriptions for ensuring that the patient does not become ill during their scheduled procedure (Gandra 2014). As a result, antibiotics have become embedded into modern society as one integral piece of medical technology that supports the capability for many other lifesaving techniques to be successfully performed with limited probability of infection-related side effects occurring in the patient.

Beyond simply being developed for human use, there were other experiments conducted by Thomas Jukes that showed young chickens fed with remnants of manufacturing antibiotics would gain approximately double the weight compared to chicks that were not, and that this difference was primarily due to the minor presence of antibiotic agents left among the remnants. The agricultural industry was ecstatic over what, on the surface, appeared to be a very cheap feed product to introduce additional nutrients for their animals. Farmers did not see any downsides to including antibiotic remnants in animal feed, so as a result a new industry of “growth-promoter antibiotics” were developed targeted at suppressing diseases in farm animals and allowing them to grow large much quicker than before the introduction of antibiotics (The Inquiry 2016). This has led to increased meat production from farm animals that humans have gladly consumed on a large scale throughout the years since, but the resultant impacts have shown up through increased prevalence of antibiotic-resistant bacteria strains around the world as well as whole farms losing their value when an infection is able to take hold and spread despite the antibiotic materials being fed to the animals.

## Issues of Resistance and Compounding Factors

The major problem with the extensive usage of antibiotics is that the microbes they are meant to fight will build up some form of resistance against those very antibiotic agents due to selective pressures over time. This is not considered unusual for the natural evolutionary processes, but the large quantities of antibiotics being used has driven the rise of major antibiotic resistance problems and corresponding superbugs such as methicillin-resistant *Staphylococcus aureus* (MRSA) and other infections common to the over-sterilized environment of hospitals. It should be noted at this point that while evolution is often considered to be a slow process occurring by accumulating minor genetic changes through multiple generations, bacteria have a very short lifespan compared to humans and thus can easily progress through multiple generations and accumulate the corresponding opportunities to develop resistance-supportive genetic changes in a matter of years. Even Fleming had acknowledged and warned about the potential of antibiotic resistance from the public abusing and overusing penicillin in 1946 (Aminov 2010; Bartlett 2013), but his warning then went ignored and similar warnings about superbugs in recent years have not yet lead to many meaningful policy changes. When considered by itself, the modern prevalence of antibiotic resistance probably would not be as much of a major issue if new classes of antibiotics were continuously being discovered to counteract the microbial development of resistance genes. However, in the current economy many companies believe that new antibiotics are too difficult to find and are also not worth the monetary investment required to conduct the research and development of additional antibiotic agents, leading to a small variety of regulated antibiotic drugs that now remain capable of treating what are otherwise considered minor illnesses and bacterial diseases instead of a well-maintained supply of targeted options.

Unlike other medicinal drugs, antibiotics are unique in that one person's usage of these agents affects how another person may respond to the same drugs due to the potential for microbes to develop resistance and transfer this resistance to other bacteria – necessitating extreme care to maintain their continued effectiveness, as even one individual's personal behavioral patterns may contribute to containing or spreading antibacterial resistance (Aminov 2010). This comes in part due to the overzealousness of pharmaceutical companies wanting to sell more drugs and increase profits, which is understandable for companies trying to make money on their original investment into developing the antibiotic drug. However, it also arises from doctors prescribing cocktails of multiple broad-spectrum antibacterial drugs against infections that are primarily caused from a narrow set of specific bacteria (Spellberg 2010). With this unnecessary overuse of precious antimicrobial agents when one targeted antibiotic could suffice, the bacteria are given many more opportunities to develop resistance against the current supply of antibiotics and driving humankind closer to relying solely on carbapenems, an antibiotic that targets Gram-negative bacteria and is reserved for cases when all other available drugs fail (Gandra 2014), and other “last-resort” drugs as a means of preventing illnesses.

A correlated factor here is the idea that patients who get sick and see their primary care physician are often instructed to complete a full course of antibiotics even if their symptoms resolve, since recurrent infections are caused by distinct bacteria strains rather than a relapse of the original antibiotic-treated strain (Spellberg 2016). While the idea of ensuring the disease has been cured may be sound, the continued use of antibiotics after the body shows recovery do increase the evolutionary pressures on remaining bacteria to develop resistance and further increases the problems arising from trying to preserve the effectiveness of last-resort antibiotics (Aminov 2010). The historical heuristics supporting the instructions for requiring completion of

a full antibiotic treatment were aimed at the idea of ensuring the illness has been cured, but modern science as a whole focuses on having evidence to build up drug use guidelines. This suggests there exist opportunities where medical practices and standards can be improved with regards to applying antimicrobial agents for treating regular diseases, and instead could be supplanted by an evidence-based policy.

Antibiotics are considered magic bullets that could target the bacteria they are effective against, but the bacteria's continued adaptations and population dynamics allow them to eventually resist the very drugs that people believed would work on them. The very nature of evolution and natural selection drives bacteria that are better suited to changing environmental factors to proliferate as generations pass, and with the vast usage of present antibiotics around the world much of the bacteria's environment consists of trying to survive against these antibacterial agents (Aminov 2010). They also operate on a population-wide network with capabilities of signaling other bacterial cells and transferring genes between each other, though many parts of these intra-cellular interactions are still not fully understood by scientists (The Inquiry 2016; Merriman 2016). It comes as no surprise then that in combination with their short lifespans, as previously mentioned, bacteria are rapidly communicating resistance genes among each other and allowing the spread of antibiotic resistance to occur with worldwide prevalence in only a number of years.

As a whole, the pharmaceutical industry had already isolated many of the "easier" sources of antibiotic agents by the 1960s, making completely new sources difficult to identify (The Inquiry 2016; Spellberg 2015). This is especially true for the class of Gram-negative bacteria, which is quite worrying for scientists because these are the forms of bacteria already resistant to natural antibody defenses and are generally considered more able to develop



antibiotic resistance and spread these genes. One related factor compounding the severity of this issue is due to strict FDA regulations on what can likely be approved for clinical trials of potential antibiotic drugs in simple cases, leaving clinicians uncertain about using new antibiotics in relatively complex infections (Spellberg 2010). Even in cases of approved antibiotics, new drugs developed are primarily modified forms of previously-discovered agents and not novel cases as was common during the 1950s explosion of antibiotics research (Aminov 2010). This limits the potential effectiveness of these new drugs to treating similar cases as those already being treated with current market antibiotics rather than developing them to attack more difficult infections like MRSA, so the bacteria have relatively fewer evolutionary jumps to mutate through before they will find a suitable resistance gene for the new antibiotic.

Beyond the issues of bacteria evolving resistance to available antibacterial agents, the current market is unfavorable towards supporting research into new antibiotics. From an economical perspective, companies no longer see any reasonable incentive to invest in discovering new antibiotics. Without any outside incentives for pursuing antibiotic development, the net present value to a company considering the option of investing towards a new antibiotic is a \$50 million loss compared to the typical investment that the company could pursue for other medicinal therapies (Bartlett 2013; Spellberg 2015). This means that over the long run the company believes they would be losing out on the value of \$50 million dollars today by working on antibiotic-related projects. This is largely due to the relatively low sales prices for short antibiotic treatments consumed by a patient, as well as an extended length of time necessary to conduct the requisite research and complete regulatory clinical trials for new antibacterial agents before any sales can be made on a working antibiotic drug. The impact of this extended length of research and development time is compounded by the fact that due to inflation money loses its

value as time passes, so a few hundred million dollars of future antibiotic sales may only be worth tens of million dollars in today's value. This projected return is often lower than the potential of developing other drugs, so many pharmaceutical companies end up making an economic decision of foregoing any work on the research and development process integral to finding new agents for treating infections (Bartlett 2013). Antibiotic research and development also has to compete with the opportunities of other medicines providing long-term therapies for cancer and similar lifelong illnesses, which can easily generate many thousands of dollars from one course of treatment for a single patient and often compute to corresponding net present values of over \$1 billion gain. According to a cost analysis comparison, antibiotics are meant to be inexpensive treatments for short-term diseases while other drugs can be sold as expensive therapies for the rest of a patient's life, so to a pharmaceutical company the potential economic value of antibiotics would at best only be derived from sacrificing the profits of other more lucrative drugs, and even then only if they truly wish to support the continued capabilities of antibacterial agents. There is simply no rational economic reason for companies to lose money for a chance to discover the next antibacterial drug when they could potentially gain billions by developing the next medicine for extended treatment, and that has driven most pharmaceutical companies out of the antibiotic market in pursuit of long-term medicines.

Antibiotic resistance is also expensive to society as a whole, not just through costs related to developing new drugs as current ones lose their efficacy. Healthcare costs that could be linked to hospital-acquired bacteria, which are often some of the most resistant strains in the world yet are not often discussed with the general public, have been estimated over \$2 billion per year in the US alone – this is more than the annual spending for influenza, a virus the public is consciously aware of and actively develops annual vaccines for prevention (Aminov 2010).

Additionally, the patients who are forced to stay in the hospital for extended lengths of time as a result of such infections will forego earnings during the extended stay but also likely require additional post-discharge care to minimize the possibilities of complications leading to deaths and other illnesses, with estimates from the year 2000 suggesting these losses may easily run over \$55 billion (Gandra 2014).

### **Preventing a Post-Antibiotic World**

Within the current framework of understanding microbial infections and antibiotic agents, it may seem like a major crisis looms on the horizon leading to a post-antibiotic world due to the multitude of issues previously discussed. However, there are still many opportunities for continuing forward and maintaining the power of antimicrobial treatments that humans have come to take for granted. It simply requires a concerted effort of people across disciplines and the general public at large working together towards a common goal, namely one aimed to revitalize efforts to discover and develop new treatments while preserving the efficacy of current antibiotic drugs. Towards this goal, I shall suggest a number of ideas which may help to prevent or at worst delay the oncoming post-antibiotic scenario.

The first set of ideas is focused on preserving the efficacy of current antibiotic drugs. One major factor is the over-prescription of these drugs to people who would not actually benefit from using them. Since people had hailed antibiotics as miracle drugs, they had often come to believe that any sickness they encounter can be cured or treated by taking some antibiotics – but this is often not the case, especially with antibiotic agents having no effect for viral infections. The public needs to be better educated about proper usage of antibiotics and work with doctors and physicians to understand why their particular sickness might not be treated with antibiotics,

thus minimizing inappropriate human usage of these valuable drugs. This education can come through online advertisement campaigns and through other channels likely to reach a majority of the public in a manner similar to the anti-tobacco campaign, and should focus on working with primary care physicians for differentiating bacterial infections, such as *E. coli* or strep throat which is caused by *Streptococcal* bacteria, from viral diseases like the common cold and influenza. It should also include helpful tips of individual practices most likely to minimize and prevent diseases from infecting members of the public such as the restroom handwashing signs, thereby applying the education idea along two approaches for reducing the usage of antibiotics. Although diagnostic technologies for distinguishing bacteria from viruses are already used in medical facilities, engineering advancements could help bring preliminary screening tools into public use alongside the education campaigns and reemphasize how antibiotics would not help treat the common cold affecting their child. Other studies have shown that peer pressure among doctors can serve as an additional safeguard against over-prescribing antibiotics to a demanding public (Merriman 2016). With commitments to sensibly serving prescriptions and including warnings in cases where antibiotics may not be effective, doctors and physicians become more willing to discuss disease details with their patients and reinforce the public education campaigns.

In addition, numerous studies not reviewed for this thesis have shown that it may be possible to shorten the antibiotic treatment regimens from a 10-day median to a 5-day median for some diseases without reducing their effectiveness (Aminov 2010; Spellberg 2016). That suggests conducting experiments for additional infections means doctors will be able to prescribe fewer antibiotics for shorter therapy durations and reduce the selective pressures towards developing resistance among any surviving infectious bacteria. Innovative treatments based on a patient-centric framework may be the best path forwards for safeguarding the utility of

remaining antibiotics against the dangers of bacteria developing resistance from overuse of these important drugs. These patient-focused treatments could also include newer point-of-care diagnostics so that the physician or doctor can better understand what is actually occurring within the patient's body besides simply relying on a patient's ability to describe their illness, and using that information to determine whether an antibiotic prescription is necessary for the patient to recover or whether a different therapy would be more appropriate.

At the current stage of drug availability, having a national database compiling infections for which certain antibiotics could be used while others are resistant would be a significant step forwards to ensuring proper usage of available antibacterial drugs. Studies conducted in the European Union based on a similar idea have shown a strong correlation between the rate of per capita antibiotic consumption and the rate of resistance observed among their member populations (Bartlett 2013). This makes sense, as increased usage of antibiotics provides the bacteria with increased opportunities to experience the antibacterial agents and evolve resistant genes to counteract the agents. With the European Union, the countries that showed better care for the overall usage of antibiotics and invested more effort to managing and regulating their availability, such as the Netherlands and more recently France, were found to be better stewards of antibiotics and showed decreased overall presence of resistance in bacteria when compared to countries like Greece that did not properly care for regulating their antibiotics usage (Bartlett 2013). These ideas of antibiotic stewardship should be applied in the United States as well, and together with public education about proper usage of antibacterial drugs will reduce the evolutionary rate of resistance to current antibiotics.

Any additional studies of antibiotic effectiveness are not likely to be very useful in practice, however, if regulatory approval standards are not accommodating of constantly

evolving needs towards treating bacterial infections. While the current stance for conducting clinical trials treat bacterial infections as simple cases with very little consideration for predisposed factors that may affect antibiotic efficacy, doctors are left uncertain about how effective the antibiotic agent may actually be for their particular patient who perhaps has a history of illnesses and had already tried a similar antibiotic, and often find no guidance for interpreting the results of FDA-required clinical trials for using the antibiotic in real-world scenarios (Bartlett 2013; Spellberg 2010). The standards should be clarified to allow for more extensive and more comprehensive trials that would account for additional factors beyond the basic question of “does this antibiotic agent work” on a particular subset of the population, including factors relating to whether race or age or medical history may play a part in determining their effectiveness. These clarifications could involve a panel of antibiotics experts, public health specialists, doctors, and operations researchers working together to find a balance between clear indications of clinical trial opportunities for focusing study of the antimicrobial agent’s effects on certain diseased patients compared to a broader understanding of its potential overall efficacy in more complicated real-world scenarios. The panel may consider approaching this work by examining current standards and determining which statistical-based requirements stifle progress for current experimental antibiotics but could be loosened to support future trials, as exemplified through requiring placebo-controlled trials for new pneumonia antibiotic treatments (Spellberg 2015). Through the clarified regulatory standards, future clinical trials would be better able to answer more questions that doctors and physicians currently have about the efficacy of real-world usage for the new antibiotics.

Regulations related to antibiotic usage for farm animals and among the environment overall must also be tightened in a manner similar to what the European Union has already

implemented as its standards, with a focus on treating infections after they have definitively sickened some animals rather than trying to prevent illnesses from occurring at all (Merriman 2016; Bartlett 2013). A reduction in agricultural use could thus reduce the proliferation of antibiotic-resistant bacteria by limiting the potential sources of developing resistance, where a 1976 study by microbiologist Stewart Levy showed that antibiotic-resistant bacteria were spreading around the farm and even to nearby humans that were not consuming those antibiotic drugs (The Inquiry 2016). Because farm animals are such a major consumer of antibiotic agents, it will require vast improvements in regulating their usage by the agriculture industry before any significant impact will be observed for overall development of antibiotic resistance. These improvements should mirror European Union standards, where antibiotics are available only for treating diseases instead of working as “growth-promoters” by suppressing potential infections, and ideally would extend towards providing better care for the animals so that they may grow to similar sizes with only minor usage of antibiotic agents. Through this method, fewer cases of resistance will develop before humans can really utilize some of the modern antibiotics while also limiting the current chances, however seemingly small, that a superbug or similar drug-resistant infection wipes out the population of multiple farms.

Even if all the prior suggestions are fully implemented, humankind still needs to identify and isolate additional genuinely new sources of antimicrobial agents to ward off many of the issues posed by antibiotic resistance. Thus, the second set of ideas is aimed towards helping scientists to realize new opportunities for attacking bacterial infections, which is the primary purpose of using antibiotic agents. Although it remains difficult to replicate any bacteria originating from “exotic” parts of the world, new technologies such as a diffusion chamber (Merriman 2016) can assist by closely recreating the original environments for the bacteria and

allowing scientists to study them under a controlled situation. Other opportunities exist from studying ecological niches beyond the traditional soil-based fungi (Aminov 2010), or possibly even attacking a completely synthetic approach based on examining genome sequences of the infectious bacteria. It should be possible to understand the unique biochemical compositions exhibited by a variety of bacteria strains, either by knowing its genome sequence or by using polymerase chain reaction (PCR) machines to examine them, so although a synthetic approach may have a broader search region than simply examining natural sources it would also offer more opportunities to consider different approaches for targeting and attacking bacteria that may not have naturally been evolved. Admittedly, other challenges to applying the synthesis-based option include ensuring sufficient supply of chemical and biological compounds to create new potential antibiotic agents and test their efficacy within a controlled experiment, so this may take more time and resources to implement compared to the other nature-based sourcing suggestions provided.

Beyond finding exotic sources of new antibiotics, scientists should investigate the possibility of developing therapies that operate on a collective population scale instead of an individual cell scale due to their capabilities of signaling and transferring genes to other bacterial cells. The traditional view of bacteria was one considering them to be simple singular-celled organisms, so antibiotics were targeted to attack the disease primarily by killing off cells or by restricting its ability to reproduce and spread. Targeting the population scale could instead focus on attacking the signaling methods or other related systems and become a more effective antimicrobial agent as the selective pressure on bacteria to adapt drug resistance in this manner would be much lower than the selective pressure to adapt against directly lethal drugs, if not completely reduced. In addition, reframing our understanding of bacterial diseases and how the



human body has already evolved to handle infections may support development of novel therapies and treatment approaches that allow the body to work through combatting the bacteria with some support of antibacterial drugs. These developments would also improve the capabilities of point-of-care diagnostics and provide physicians with more choices to consider for treating their patient's illness instead of simply prescribing a round of antibiotic therapy due to there being no other option.

The research necessary for developing new antibacterial agents can be funded through some economic incentives to pharmaceutical companies, either as push incentives supporting the research and development stages, such as through tax breaks, or as pull incentives allowing for extended sales protection. Some models examined by Spellberg et al. showed that when the time value of money is accounted for, a pull incentive allowing for five years of extended sales exclusivity after the normal twenty year patent term expires would generate equivalent economic value as a push incentive investment of \$43 million right away, or equivalent to providing \$6.25 million each year during the typical thirteen-year research and development period of antibiotic drugs (Spellberg 2012). The tradeoffs here come from pull incentives benefitting solely the company and depending on the premise of increased sales during extended exclusivity, which go against the stewardship need for properly protecting and limiting usage of antibiotics as short-term treatments, while push incentives likely will require considerable public force of will to dedicate the tax breaks or other form of economic support towards developing new antibiotic drugs rather than investing in other public works projects such as education and transportation. Other options for incentivizing research and development of antibiotic drugs could include working through public-private partnerships as well as using the defense contractor funding model, where government agencies fund part of the costs for research and development in

exchange for telling the contractor companies what public needs the research should focus on (Bartlett 2013; Spellberg 2015). This option is likely the most prudent opportunity to emphasize the public trust nature of antibiotics as a whole and support the notion that even though private companies are putting forth much of the effort to conduct research and development of new antibiotics, the resulting drugs need to be cared for per proper stewardship concerns as a publically-shared commodity with distribution regulated by patients being given doctor prescriptions suited with an effective antibiotic choice and at an efficient dosage for treatment of a properly diagnosed disease, instead of being considered as simply another set of medical supplies available that the general public can stock at home for unexpected illnesses.

## **Conclusions**

This thesis examined the history of antibiotics and suggested a consortium of methods for preserving their capabilities and efficacy, but the research work will never fully be complete for humanity since bacteria and evolution are such fundamental aspects of nature. So long as humankind desires to maintain the current style of medical care, with antibiotics usage prevalent across many fields as a preventative measure against potential diseases, the race to find the next big drug before bacteria develop resistance to the current one continues moving onwards with significant economic impacts. Even on a population level, there are still many factors and questions about antibiotics that remain unknown, especially with regards to how antibiotics and their corresponding resistance effects the environment as a whole – can they spread from humans back into the food chain, for example, or would they readily disseminate across the broader world of nature and create new superbugs among bacteria that scientists currently do not know about, for another. Should this thesis help influence a party's decision for studying antibiotics

and managing the stewardship of these miracle drugs, future work in this area could examine these interactions of antibiotic resistance among the environment at large or how bacteria manage to coordinate on a population scale, as well as the possibility of conducting macroeconomic cost-benefit analyses for implementing any of the multitude of policies aimed towards preserving antibiotics. The work geared for understanding microbes and attacking agents is never-ending due to the continuous evolution of resistance, but it is imperative for humanity to take important steps now to help preserve the capabilities of current antibiotics while waiting for new ones to be discovered and produced. Otherwise, humankind may fall down to a world comprised of shorter lifespans and “simple” illnesses becoming deadly to humans once again, losing much of the medical progress and quality of life advancements that were made with the discovery and isolation of antibiotics.

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